Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies

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Abstract

Coronavirus disease 2019 (COVID-19), caused by the novel human coronavirus SARS-CoV-2, is currently a major threat to public health worldwide. The viral spike protein binds the host receptor angiotensin-converting enzyme 2 (ACE2) via the receptor-binding domain (RBD), and thus is believed to be a major target to block viral entry. Both SARS-CoV-2 and SARS-CoV share this mechanism. Here we functionally analyzed the key amino acid residues located within receptor binding motif of RBD that may interact with human ACE2 and available neutralizing antibodies. The in vivo experiments showed that immunization with either the SARS-CoV RBD or SARS-CoV-2 RBD was able to induce strong clade-specific neutralizing antibodies in mice; however, the cross-neutralizing activity was much weaker, indicating that there are distinct antigenic features in the RBDs of the two viruses. This finding was confirmed with the available neutralizing monoclonal antibodies against SARS-CoV or SARS-CoV-2. It is worth noting that a newly developed SARS-CoV-2 human antibody, HA001, was able to neutralize SARS-CoV-2, but failed to recognize SARS-CoV. Moreover, the potential epitope residues of HA001 were identified as A475 and F486 in the SARS-CoV-2 RBD, representing new binding sites for neutralizing antibodies. Overall, our study has revealed the presence of different key epitopes between SARS-CoV and SARS-CoV-2, which indicates the necessity to develop new prophylactic vaccine and antibody drugs for specific control of the COVID-19 pandemic although the available agents obtained from the SARS-CoV study are unneglectable.